SUPPORT FOR THE AMENDMENTS

Claims 1-38 and 43-49 were previously canceled.

Claims 39 and 41 have been amended.

The amendment to Claims 39 and 41 is supported by original Claims 22-29 and the specification as filed, for example, at pages 16-18, page 21, and the Examples.

No new matter has been added by the present amendment.

REMARKS

Claims 39-42 and 50-56 are pending in the present application.

The rejection of Claims 39-42 and 50-56 under 35 U.S.C. §112, first paragraph (enablement), is respectfully traversed.

In the Office Action, the Examiner acknowledges that the claimed invention is enabled for the tumor form exemplified (Malignant fibrous histiocytoma MT-9). But, the Examiner contends the state of the art is unpredictable in terms of the treatment of the wide variety of tumors embraced by the claimed invention and the specification fails to provide sufficient guidance as to how tumors can be treated. Allegedly to support this contention, the Examiner cites Li et al ("Discovery and Development of Antimitotic Agents that Inhibit Tubulin Polymerisation for the Treatment of Cancer", *Expert Opin. Ther. Patents* (2002), 12(11): 1663-1702).

To this end, the Examiner characterizes AC-7700 as an antimitotic agents with tubulin binding sites. On page 1664-5, Li et al also disclose that "antimitotic agents are not truly selective antitumor agents since disruption of the mitotic spindle will affect all dividing cells... As cancer cells proliferate more rapidly than most normal human cells, antimitotic agents are expected to kill cancer cells preferentially. Truly selective cancer chemotherapy, in which a drug will specifically destroy malignant tumour cells, is the ultimate goal of cancer research". At page 1667, Li et al disclose that combretastitins (citing combretastatin A-4 (compound 20)) shows "poor efficacy in vivo due, in part, to its poor water solubility and pharmacokinetic properties". The Examiner cites pages 1668 and 1691 of Li et al and argues "AC-7700 even though it exhibits good in vivo efficacy against several advance solid tumors it is noted that the tubulin binding agents appear to fail in human trials despite demonstrating

good preclinical efficacy. One reason appears to be a large difference between the tolerated dosages in human clinical trials and those determined in the preclinical animal models".

In making these assertions and drawing the corresponding conclusions, it appears that the Examiner is mistakenly substituting the results of other combretastitins (e.g., AC-7739 on page 1668) and gross generalizations of the class as a whole (e.g., page 1691) to allege that AC-7700 would also not work for tumor treatment *in vivo*. However, Applicants submit that this selective citation of Li et al and unsupported overgeneralizations are incorrect. This is important in this case as Li et al actually contradicts the Examiner allegations. Specifically, on page 1668, Li et al specifically address AC-7700 stating:

> "The serine prodrug, compound 30 (AC-7700, HCl salt), exhibits good in vivo efficacy against several advanced solid tumours and orthotopically transplanted tumours. The *in vivo* efficacy, as well as antivascular and antimitotic effects of AC-7700 were evaluated side by side with several colchicine site binders (Table 1). AC-7700 strongly suppressed the growth of colon 26 adenocarcinoma with significant reduction in tumour perfusion, while CA4P showed a moderate efficacy and antivascular effect. In contrast, vinblastine (200) achieved better efficacy than AC-7700 without causing significant suppression of tumour perfusion. Interestingly both AC-7700, and to a lesser extent CA4P, are capable of inducing marked reduction in tumour blood perfusion below their MTD. AC-7700 remained equally effective against both wild type and resistant strains of colon 26 *in vivo*, despite being tenfold less active against the resistant cell lines *in vitro*. Therefore, AC-7700 appears to exert an *in vivo* antitumour activity mainly through its antivascular effect and independent of its direct cytotoxiciity on tumour cells and the host's immune status. AC-7700 is in Phase I clinical trials by Aventis Pharmaceuticals under a new code, AVE8062A... **AVE8062A was efficacious against a large panel of *in vivo* advanced (~200 mg) and late-stage (~500 mg) tumour models including human colon (HCT-8 and LoVo), mammary (MX-1), prostate (PC-3) and melanoma (B16)**" (emphasis added)

Based on the foregoing, Li et al actually supports the position that AC-7700 is effective for treating tumors beyond the exemplified tumor cells (Malignant fibrous histiocytoma MT-9).

Additional evidence that shows that AC-7700 is efficacious toward treatment of a broader scope of tumors *in vivo* is provided by the following references:

1) US 5,525,632;

2) US 5,731,353;

3) US 5,674,906;

4) US 6,462,087;

5) Kim et al, Cancer Res. 2007 Oct 1; 67(19): 9337-45;

6) Ohno et al, Int. J. Clin. Oncol. 2002 Jun; 7(3): 171-6;

7) Hori et al, Br. J. Cancer. 2002 May 20; 86(1): 1604-14;

8) Hori et al, Med. Sci. Monit. 2001 Jan-Feb; 7(1): 26-33;

9) Nihei et al, Jpn. J. Cancer Res. 1999 Sep; 90(9): 1016-1025;

10) Hori et al, Cancer Sci. 2008 Jul; 99(7):1485-91. Epub 2008 Apr 29;

11) Hori et al, Eur. J. Cancer. 2003 Sep; 39(13): 1957-66;

12) Morinaga et al, Cancer Sci. 2003 Feb; 94I(2):200-4;

13) Lavisse et al, Invest. Radiol. 2008 Feb; 43(2): 100-11 (PMID: 18197062);

14) Hori et al, Br. J. Cancer. 2003 Oct 6; 89(7): 1334-44;

15) Nihei et al, Jpn. J. Cancer Res. 1999 Dec; 90(12): 1387-95; and

16) Hori et al, Jpn. J. Cancer Res. 1999 Sep; 80(9): 1026-38.

Applicants submit that references (5)-(9) show an anti-tumor effect on various experimental tumors. References (10)-(12) show the synergistic effect of AC-7700 in combination with preexisting treatments such as radiation and anti-tumor drug(s) and show the efficacy of AC-7700 for cancers to which the preexisting treatment is applied. References (13)-(16) show the mechanism of action of AC-7700 and suggest that the

therapeutic effect is independent of type, site, malignancy, etc. of the cancer and may be produced due to blood flow interruption to the tumor.

In view of the foregoing, Applicants submit that skilled artisan would appreciate how to make and use the invention as claimed. Further, the artisan would have a reasonable expectation that the claimed method for treatment of tumors would extend beyond the tumor form exemplified (Malignant fibrous histiocytoma MT-9). As such, Applicants submit that the claimed invention is enabled as required by 35 U.S.C. §112, first paragraph.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 1, 11-15, 30, 32, 35-42, and 44-48 under 35 U.S.C. §103(a) over Nihei et al with Hori et al in view of Fex et al and Sugawara et al are is respectfully traversed.

In the Office Action mailed June 17, 2008, the Examiner has maintained that the claims are obvious over the combined disclosures of Nihei et al, Hori et al, Fex et al, and Sugawara et al. The Examiner's restatement of the grounds of rejection on pages 5-8 of the Office Action are just that – a restatement. Indeed, the Examiner's statement of the grounds of rejection is virtually identical, but for the addition of a couple structures, to the rejection appearing in the Office Action mailed September 11, 2007, even to the extent that the Examiner still makes reference to canceled Claims 1, 30, 32, and 35. Regardless, Applicants disagree with the Examiner's allegation that the claimed invention would be obvious in view of the combined disclosures of Nihei et al, Hori et al, Fex et al, and Sugawara et al.

The claimed invention relates to a method for treatment of tumors, which comprises administering to a subject in need thereof a composition comprising (a) an effective amount of an anti-inflammatory active substance, wherein the anti-inflammatory active substance is a

Dexamethasone selected from the group consisting Dexamethasone, an ester of Dexamethasone, and a salt of Dexamethasone; and (b) (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide or a salt thereof (see Claim 39). Applicants submit that this invention is not obvious over Nihei et al with Hori et al in view of Fex et al and Sugawara et al.

As discussed on pages 1-3 of the specification, tubulin polymerization-inhibitory active substances (e.g., (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide ("AC-7700") have a relatively narrow safety zone between lethal dose and effective dose. Therefore, there are practical and very real limitations on the medicinal use of AC-7700. For the first time, the present Applicants have shown that the safety zone of AC-7700 can be expanded while maintaining anti-tumor effect. To this end, Applicants discovered that the specific combination of the anti-inflammatory active substance "Dexamethasone" reduced the toxicity of AC-7700. The Examiner makes no attempt to address this very important limitation nor has the Examiner provided any explanation as to why one of skill in the art would have found it obvious to combine AC-7700 with the dexamethasones of the present invention without fear of either (a) loss of anti-tumor effect or (b) increased toxicity.

Further, Applicants remind that as set forth in MPEP §716.02(a) "greater than expected results are evidence of nonobviousness." Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

In the present case, Applicants have demonstrated in Figures 1 and 2 (see section (6)(1) on page 24) the reduction of AC-7700 toxicity with Dexamethasone. For the Examiner's convenience, Figures 1 and 2 are reproduced below:

Fig.1

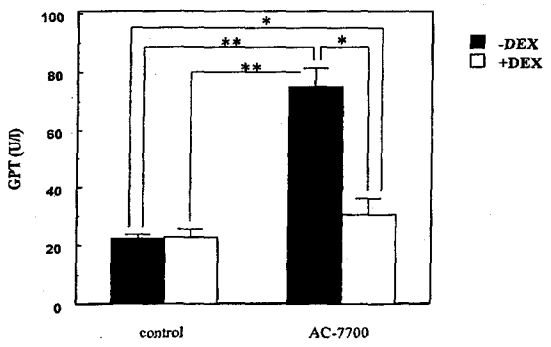

Fig.2

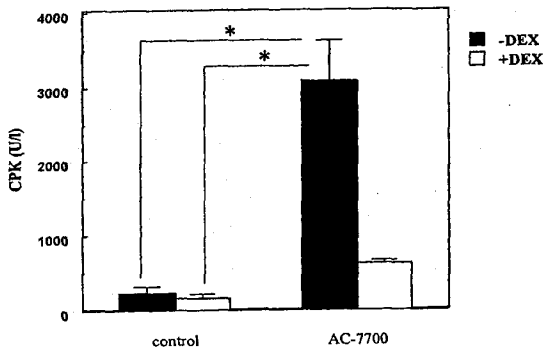

Figure 1 shows results from the toxicity test with tumor-bearing rats from Example 1 (Scheffe's F test; *p<0.05, **p<0.01) F344 rats subcutaneously transplanted MT-9 tumor / Dexamethasone (1mg/kg)/AC-7700 (10mg/kg); Blood biochemical indices: GPT; ■: - DEX; □: + DEX. Figure 2 shows results from the toxicity test with tumor-bearing rats in Example 1 (Scheffe's F test; *p<0.05). F344 rats subcutaneously transplanted MT-9 tumor / Dexamethasone (1mg/kg)/AC-7700 (10mg/kg); Blood biochemical indices: CPK; ■ : - DEX; □ : + DEX.

The results reveal that Dexamethasone had remarkably reduced the toxicity of AC-7700 (10mg/kg), hepatic toxicity (GPT) and cardiovascular toxicity (CPK) in tumor bearing rats. Concerning the gastrointestinal toxicity, the combined use of Dexamethasone with AC-

7700 has revealed that diarrhea induced by AC-7700 in mice was significantly improved. The toxicity was unexpectedly and significantly improved.

However, if the combination significantly reduces the pharmaceutical effect on anti-tumor simultaneously (reduction of toxicity), it is meaningless and worthless because the safety zone of AC-7700 is not expanded. Applicants discovered that even if both the AC-7700 and Dexamethasone were administered, there was no significant deference in the pharmaceutical effect between AC-7700 alone and combination of AC-7700 and Dexamethasone as shown in Table 1 (below).

[Table 1] Influence of Dexamethasone on the pharmaceutical effect of AC-7700

DEX(mg/kg/day)	AC-7700(mg/kg/day)	I.R.(%)
0	0	0
0	10	84**
1	0	21
1	10	72**

(Note: Mann-Whitney's U test; **: $p<0.01$ vs. Control)

Nihei et al disclose that "AC-7700 (a) maintained activity against solid tumor growth when combined with Dexamethasone", but this means activity is maintained. The present inventors surprising found that the combination of AC-7700 and Dexamethasone improves safety zone of AC-7700 significantly, so at least such a combination is very worthy and valuable in practical use of AC-7700. Such effects of the combination are not disclosed and not suggested in the prior arts and advantageous effects are unpredictable.

Applicants submit that at the time that this application was filed, it was unknown that a combination tublin polymerization inhibitory active agent (AC-7700) and anti-inflammatory active substance (Dexamethasone) expands the narrow safety zone of tublin polymerization inhibitory active agent. Thus, Applicants submit that the present invention would not be obvious.

Although acknowledging that the foregoing results are unexpected, the Examiner largely disregards the evidence in Figures 1 and 2 for the claimed invention alleging that the results are not commensurate in scope. Specifically, the Examiner notes that the results are only provided for the combination of (a) AC-7700 and dexamethasone and (b) for the treatment of Malignant fibrous histiocytoma, MC-9. With respect to (a), Applicants submit that these results are representative of the claimed invention as each of the claimed forms of Dexamethasone (Dexamethasone, an ester of Dexamethasone, and a salt of Dexamethasone) still contain the dexamethasone structure. Further, with respect to (b), Applicants submit that in view of the discussion above relating to the scope of tumors in which AC-7700 is effective, the results above would be applicable to more that just the treatment of Malignant fibrous histiocytoma, MC-9. As such, Applicants submit that the results above would rebut even a prima facie case of obviousness.

Withdrawal of these grounds of rejection is requested.

The objection to Claim 39 is obviated by amendment. To ensure clarity, Claim 39 has been amended such that part (b) only recites "(Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide or a salt thereof". Withdrawal of this ground of objection is requested.

Applicants submit that the present application is now in condition for allowance.

Early notice to this effect is earnestly solicited.

Respectfully submitted,

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